



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 882

[Docket No. FDA-2014-N-1209]

Neurological Devices; Reclassification of Cranial Electrotherapy Stimulator Intended to Treat Insomnia and/or Anxiety; Effective Date of Requirement for Premarket Approval for Cranial Electrotherapy Stimulator Intended to Treat Depression

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed order.

SUMMARY: The Food and Drug Administration (FDA) is issuing a proposed administrative order to reclassify the cranial electrotherapy stimulator (CES) devices intended to treat insomnia and/or anxiety, a preamendments class III device, into class II (special controls) and subject to premarket notification, and to require the filing of a premarket approval application (PMA) for CES devices intended to treat depression. FDA is proposing the reclassification of CES devices intended to treat insomnia and/or anxiety under the Federal Food, Drug, and Cosmetic Act (the FD&C Act) based on new information pertaining to the device. This proposed action would implement certain statutory requirements. FDA is also clarifying the identification for CES devices in this proposed order by identifying CES as a prescription device that applies electrical current that is not intended to induce a seizure to a patient's head to treat psychiatric conditions. This clarification distinguishes CES from electroconvulsive therapy (ECT).

DATES: Submit either electronic or written comments on this proposed order by [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]. See

sections IX and XVII of this document for, respectively, the proposed dates when the new requirements apply and the proposed effective date of a final order based on this proposed order.

ADDRESSES: You may submit comments as follows:

#### Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <http://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <http://www.regulations.gov>.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

#### Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

- For written/paper comments submitted to the Division of Dockets Management, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2014-N-1209 for "Neurological Devices; Reclassification of Cranial Electrotherapy Stimulator (CES) Intended to Treat Insomnia and/or Anxiety; Effective Date of Requirement for Premarket Approval for CES Intended to Treat Depression." Received comments will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at <http://www.regulations.gov> or at the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION". The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <http://www.regulations.gov>. Submit both copies to the Division of Dockets Management. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed

except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at:

<http://www.fda.gov/regulatoryinformation/dockets/default.htm>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <http://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Michael Ryan, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, rm. 1615, Silver Spring, MD 20993, 301-796-6283, [michael.ryan@fda.hhs.gov](mailto:michael.ryan@fda.hhs.gov).

#### SUPPLEMENTARY INFORMATION:

##### I. Background--Regulatory Authorities

The FD&C Act, as amended by the Medical Device Amendments of 1976 (the 1976 amendments) (Pub. L. 94-295), the Safe Medical Devices Act of 1990 (SMDA) (Pub. L. 101-629), Food and Drug Administration Modernization Act of 1997 (FDAMA) (Pub. L. 105-115), the Medical Device User Fee and Modernization Act of 2002 (MDUFMA) (Pub. L. 107-250), the Medical Devices Technical Corrections Act (Pub. L. 108-214), the Food and Drug Administration Amendments Act of 2007 (Pub. L. 110-85), and the Food and Drug Administration Safety and Innovation Act (FDASIA) (Pub. L. 112-144), among other amendments, establishes a comprehensive system for the regulation of medical devices intended for human use. Section 513 of the FD&C Act (21 U.S.C. 360c) established three categories

(classes) of devices, reflecting the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. The three categories of devices are class I (general controls), class II (special controls), and class III (premarket approval).

Under section 513(d) of the FD&C Act, devices that were in commercial distribution before the enactment of the 1976 amendments, May 28, 1976 (generally referred to as preamendments devices), are classified after FDA has: (1) Received a recommendation from a device classification panel (an FDA advisory committee); (2) published the panel's recommendation for comment, along with a proposed regulation classifying the device; and (3) published a final regulation classifying the device. FDA has classified most preamendments devices under these procedures.

Devices that were not in commercial distribution prior to May 28, 1976 (generally referred to as postamendments devices) are automatically classified by section 513(f) of the FD&C Act into class III without any FDA rulemaking process. Those devices remain in class III and require premarket approval unless, and until, the device is reclassified into class I or II or FDA issues an order finding the device to be substantially equivalent, in accordance with section 513(i) of the FD&C Act, to a predicate device that does not require premarket approval. The Agency determines whether new devices are substantially equivalent to predicate devices by means of premarket notification procedures in section 510(k) of the FD&C Act (21 U.S.C. 360(k)) and part 807 (21 CFR part 807).

A preamendments device that has been classified into class III and devices found substantially equivalent by means of premarket notification (510(k)) procedures to such a preamendments device or to a device within that type (both the preamendments and substantially equivalent devices are referred to as preamendments class III devices) may be marketed without

submission of a PMA until FDA issues a final order under section 515(b) of the FD&C Act (21 U.S.C. 360e(b)) requiring premarket approval.

Although under the FD&C Act the manufacturer of a preamendments class III device may respond to the call for PMAs by filing a PMA or a notice of completion of a product development protocol (PDP), in practice the option of filing a notice of completion of a PDP has not been used. For simplicity, although corresponding requirements for PDPs remain available to manufacturers in response to a final order under section 515(b) of the FD&C Act, this document will refer only to the requirement for the filing and receiving approval of a PMA.

On July 9, 2012, FDASIA was enacted. Sections 608(a) and (b) of FDASIA (126 Stat. 1056) amended sections 513(e) and 515(b) of the FD&C Act, changing the mechanism for, respectively, reclassifying a device and requiring premarket approval for a preamendments class III device from rulemaking to an administrative order.

#### A. Reclassification

FDA is publishing this document to propose the reclassification of CES devices to treat insomnia and/or anxiety from class III to class II.

Section 513(e) of the FD&C Act provides that FDA may, by administrative order, reclassify a device based upon "new information." FDA can initiate a reclassification under section 513(e) of the FD&C Act or an interested person may petition FDA to reclassify a preamendments device. The term "new information," as used in section 513(e) of the FD&C Act, includes information developed as a result of a reevaluation of the data before the Agency when the device was originally classified, as well as information not presented, not available, or not developed at that time. (See, e.g., Holland-Rantos Co. v. United States Department of Health,

Education, and Welfare, 587 F.2d 1173, 1174 n.1 (D.C. Cir. 1978); Upjohn v. Finch, 422 F.2d 944 (6th Cir. 1970); Bell v. Goddard, 366 F.2d 177 (7th Cir. 1966).)

Reevaluation of the data previously before the Agency is an appropriate basis for subsequent regulatory action where the reevaluation is made in light of newly available regulatory authority (see Bell, 366 F.2d at 181; Ethicon, Inc. v. FDA, 762 F. Supp. 382, 388-391 (D.D.C. 1991)), or in light of changes in "medical science." (Upjohn, 422 F.2d at 951). Whether data before the Agency are old or new data, the "new information" to support reclassification under section 513(e) must be "valid scientific evidence," as defined in section 513(a)(3) of the FD&C Act and § 860.7(c)(2) (21 CFR 860.7(c)(2)). (See, e.g., General Medical Co. v. FDA, 770 F.2d 214 (D.C. Cir. 1985); Contact Lens Mfrs. Ass'n v. FDA, 766 F.2d 592 (D.C. Cir. 1985), cert. denied, 474 U.S. 1062 (1986).)

FDA relies upon "valid scientific evidence" in the classification process to determine the level of regulation for devices. To be considered in the reclassification process, the "valid scientific evidence" upon which the Agency relies must be publicly available. Publicly available information excludes trade secret and/or confidential commercial information, e.g., the contents of a pending PMA. (See section 520(c) of the FD&C Act (21 U.S.C. 360j(c)).)

Section 513(e)(1) of the FD&C Act sets forth the process for issuing a final order for reclassifying a device. Specifically, prior to the issuance of a final order reclassifying a device, the following must occur: (1) Publication of a proposed order in the Federal Register; (2) a meeting of a device classification panel described in section 513(b) of the FD&C Act; and (3) consideration of comments to a public docket. To meet these requirements, FDA has held a meeting of a device classification panel described in section 513(b) of the FD&C Act with

respect to CES devices and is publishing in the Federal Register this proposed order to reclassify CES devices intended to treat insomnia and/or anxiety.

FDAMA added section 510(m) to the FD&C Act. Section 510(m) of the FD&C Act provides that a class II device may be exempted from the premarket notification requirements under section 510(k) of the FD&C Act if the Agency determines that premarket notification is not necessary to provide reasonable assurance of safety and effectiveness of the device. FDA has determined that premarket notification is necessary to provide reasonable assurance of safety and effectiveness of CES devices intended for treating insomnia and/or anxiety and, therefore, this device type is not exempt from premarket notification requirements.

#### B. Requirement for Premarket Approval Application

FDA is proposing to require PMAs for CES devices intended to treat depression. Section 515(b)(1) of the FD&C Act sets forth the process for issuing a final order requiring PMAs. Specifically, prior to the issuance of a final order requiring premarket approval for a preamendments class III device, the following must occur: (1) Publication of a proposed order in the Federal Register; (2) a meeting of a device classification panel described in section 513(b) of the FD&C Act; and (3) consideration of comments from all affected stakeholders, including patients, payors, and providers. FDA has held a meeting of a device classification panel described in section 513(b) of the FD&C Act with respect to CES devices and is publishing in the Federal Register this proposed order calling for PMAs for CES devices intended to treat depression.

Section 515(b)(2) of the FD&C Act provides that a proposed order to require premarket approval shall contain: (1) The proposed order, (2) proposed findings with respect to the degree of risk of illness or injury designed to be eliminated or reduced by requiring the device to have



an approved PMA or a declared completed PDP and the benefit to the public from the use of the device, (3) an opportunity for the submission of comments on the proposed order and the proposed findings, and (4) an opportunity to request a change in the classification of the device based on new information relevant to the classification of the device.

Section 515(b)(3) of the FD&C Act provides that FDA shall, after the close of the comment period on the proposed order, consideration of any comments received, and a meeting of a device classification panel described in section 513(b) of the FD&C Act, issue a final order to require premarket approval or publish a document terminating the proceeding together with the reasons for such termination. If FDA terminates the proceeding, FDA is required to initiate reclassification of the device under section 513(e) of the FD&C Act, unless the reason for termination is that the device is a banned device under section 516 of the FD&C Act (21 U.S.C. 360f).

Under section 501(f) of the FD&C Act (21 U.S.C. 351(f)), a preamendments class III device may be commercially distributed without a PMA until 90 days after FDA issues a final order (or a final rule issued under section 515(b) of the FD&C Act prior to the enactment of FDASIA) requiring premarket approval for the device, or 30 months after final classification of the device under section 513 of the FD&C Act, whichever is later. For CES devices, the preamendments class III devices that are the subject of this proposal, the later of these two time periods is the 90-day period. Since these devices were classified in 1979, the 30-month period has expired (44 FR 51770, September, 4, 1979). Therefore, if the proposal to require premarket approval for CES devices to treat depression is finalized, section 501(f)(2)(B) of the FD&C Act requires that a PMA for such device be filed within 90 days of the effective date of the final order. However, FDA does not intend to enforce compliance with the 90-day deadline for PMA

submissions for currently legally marketed CES devices to treat depression. See further discussion in section IX "Dates New Requirements Apply" for proposed compliance dates.

Also, a preamendments device subject to the order process under section 515(b) of the FD&C Act is not required to have an approved investigational device exemption (IDE) (see part 812 (21 CFR part 812)) contemporaneous with its interstate distribution until the date identified by FDA in the final order requiring the filing of a PMA for the device. At that time, an IDE is required only if a PMA has not been filed. If the sponsor, manufacturer, or importer of the device submits an IDE application and FDA approves it, the device may be distributed for investigational use. If a PMA is not filed by the later of the two dates (i.e., 180 days after the effective date of the final order), and the device is not distributed for investigational use under an IDE, the device is deemed to be adulterated within the meaning of section 501(f)(1)(A) of the FD&C Act, and subject to seizure and condemnation under section 304 of the FD&C Act (21 U.S.C. 334) if its distribution continues. Other enforcement actions include, but are not limited to, the following: Shipment of devices in interstate commerce will be subject to injunction under section 302 of the FD&C Act (21 U.S.C. 332), and the individuals responsible for such shipment will be subject to prosecution under section 303 of the FD&C Act (21 U.S.C. 333). In the past, FDA has requested that manufacturers take action to prevent the further use of devices for which no PMA or PDP has been filed and may determine that such a request is appropriate for the class III devices that are the subject of this proposed order, if finalized.

In accordance with section 515(b)(2)(D) of the FD&C Act, interested persons are being offered the opportunity to request reclassification of CES devices to treat depression.

## II. Regulatory History of the Device

In 1978, the Neurological Devices Panel (the 1978 Panel) discussed the original classification for the CES device at two separate meetings (43 FR 55716, November 28, 1978). The 1978 Panel ultimately recommended that the device be classified into class III because the safety and effectiveness of the device had not been demonstrated. The 1978 Panel considered, among other data, information from the National Research Council, which reviewed 88 published studies on CES and concluded that the device had not been shown to be effective in treating any of the conditions for which it was prescribed. In addition, the 1978 Panel indicated that there was insufficient information to establish an adequate performance standard for CES because the characteristics of the electrical current necessary for potential effectiveness were not known. The 1978 Panel believed that general controls would not provide sufficient control over these characteristics, and that the device presented a potential unreasonable risk of illness or injury to the patient if the practitioner relied on the device instead of more conventional treatment, and the device was ineffective in treating any of the conditions for which it was prescribed. FDA agreed with the 1978 Panel's recommendation, and the CES device was classified into class III in 1979 (44 FR 51770, September 4, 1979).

In support of a subsequent proposed rule in 1993 to require PMAs for CES devices (58 FR 45865, August 31, 1993), FDA performed a literature review and identified additional studies that had been conducted on the use of CES. After a review of the scientific literature, FDA concluded that the effectiveness of CES had still not been established by adequate valid scientific evidence. On August 24, 1995, FDA issued a final rule requiring PMAs (60 FR 43967), but later proposed to revoke the call for PMAs because the Agency had received new information and wanted to reconsider the classification of CES and put out a call for information (62 FR 4023,

January 28, 1997) under section 515(i) of the FD&C Act. The Agency subsequently revoked the call for PMAs (62 FR 30456, June 4, 1997).

On April 9, 2009, FDA published a notice for the submission of safety and effectiveness information on CES devices (74 FR 16214). In response to that order, FDA received information in support of reclassification from five device manufacturers that all recommended CES devices be reclassified to class II. The manufacturers stated that safety and effectiveness of these devices may be assured by limited postmarket surveillance; adequate instructions for use, including warnings about the possibility of unsafe use; availability only upon the order of a health care professional licensed to diagnose and differentiate the primary indications of CES for anxiety, insomnia, and depression from other disorders (i.e., prescription use device); and compliance with voluntary consensus standards (e.g., for electrical safety, biocompatibility, etc.).

On August 8, 2011, FDA published a proposed rule under section 515(b) of the FD&C Act proposing to require PMAs for CES devices (76 FR 48062). In developing the proposed rule, FDA considered literature on CES devices published since the previous 1993 proposed rule and the information provided in response to the 2009 notice. FDA concluded from the review of the scientific literature that the effectiveness of CES had not been established by adequate valid scientific evidence and the 1978 Panel's original class III recommendation remained appropriate. The August 8, 2011, proposed rule also provided an opportunity for interested persons to submit comments on the proposed rule and the Agency's findings. Under section 515(b)(2) of the FD&C Act, FDA also provided an opportunity for interested persons to request a change in the classification of the devices based on new information relevant to its classification. Any petition requesting a change in classification of the CES device was

required to be submitted by August 23, 2011. The comment period for the proposed rule closed on November 7, 2011.

FDA received three petitions conforming to the requirements of § 860.123 (21 CFR 860.123) requesting a change in the classification of CES devices. Of these petitions, one requested the Agency to reclassify CES devices from class III to class II for the treatment of "insomnia, depression, or anxiety." The second reclassification petition presented a more focused indication, requesting the Agency to reclassify CES devices from class III to class II for the "treatment of depression, anxiety, and insomnia in adult substance abuse patients who have failed to achieve satisfactory improvement from one prior antidepressant or sleep medication at or above the minimal effective dose and duration in the current episode, or are unable to tolerate such medication." The third reclassification petition requested the Agency to reclassify CES devices from class III to class II for the "general treatment of anxiety, depression, and insomnia as part of an approved program of medical care when conventional approaches have failed or are deemed inappropriate" and "for the treatment of the primary symptoms of substance abuse: anxiety, depression, and insomnia when conventional approaches have failed or are deemed inappropriate."

Consistent with the FD&C Act as it existed at the time, on February 10, 2012, FDA referred the reclassification petitions to the Neurological Devices Panel (the 2012 Panel) for its recommendation on the requested change in classification. FDA provided the 2012 Panel members with the three reclassification petitions and FDA's executive summary, which included an updated review of the available scientific literature on the CES device (Ref. 1). Based on its review of the data as well as information presented during an open meeting (Ref. 2), the majority of the 2012 Panel did not think there was valid scientific evidence supporting effectiveness for

treatment of insomnia, depression, or anxiety. However, three 2012 Panel members, including the industry and patient representatives, did believe there was valid scientific evidence of effectiveness, and a fourth member believed effectiveness had been demonstrated for treatment of anxiety but not for insomnia or depression. The 2012 Panel also pointed out that there was a lack of device risk, meaning that a benefit/risk analysis might be favorable with any demonstrated effectiveness. The majority of the 2012 Panel, however, recommended that CES should be kept in class III. The class III recommendation from the 2012 Panel also applied to the more focused indication of the two petitioners that requested class II for use in the substance abuse population, which is an indication outside the scope of the current classification effort as CES devices have not been cleared for use in this patient population. The 2012 Panel did not consider, however, the possibility of splitting different indications into different classifications (though one 2012 Panel member did state that there seemed to be effectiveness for treatment of anxiety), or whether there is sufficient evidence to establish clinical performance testing as a special control. The Agency has since considered these possibilities, as discussed in this document.

FDA later issued a proposed administrative order to comply with the new procedural requirement created by FDASIA when requiring PMAs for a preamendments class III device (78 FR 20268, April 4, 2013). The proposed order provided for a comment period that was open until May 6, 2013. FDA received approximately 100 comments related to the CES device, most suggesting that the device should be reclassified from class III to class II considering the limited safety risks associated with the device and the ability to establish special controls to mitigate the risks to health. FDA also received one additional reclassification petition requesting that the device be reclassified from class III to class II.

On June 12, 2014, FDA withdrew the proposed rule and proposed order calling for PMAs for CES, stating in the Federal Register notice (79 FR 33712) that the Agency had received over 300 comments to the docket in response to the proposed rule and proposed order related to CES devices. Comments that expressed an opinion about the classification of CES devices were usually in favor of a class II designation. Some comments did not openly state an opinion, but included arguments against the proposed rule or order that could reasonably be interpreted as support for a class II designation. There were also comments that agreed with a class III designation. The withdrawal also stated that FDA has considered the information before the Agency, including the deliberations of the 2012 Panel and the reclassification petitions submitted for these devices, and has determined that there is sufficient information to establish special controls, and that these special controls, together with general controls, will provide a reasonable assurance of safety and effectiveness for CES devices intended to treat insomnia and/or anxiety.

### III. Device Description

A CES device is currently defined as a device that applies electrical current to a patient's head to treat insomnia, depression, or anxiety. FDA is proposing in this order to modify the identification language from how it is presently written in § 882.5800(a) (21 CFR 882.5800(a)) for additional clarification. FDA is clarifying in the identification that these are prescription devices and that the electrical current should not be intended to induce a seizure in patients. Clarifying that the stimulation is specifically not intended to induce a seizure makes a more definitive distinction between CES and ECT devices. However, FDA does not intend to otherwise describe the stimulation or electrode placement in the definition. Existing CES technology encompasses a range of stimulation settings and electrode placements, and with

supportive clinical data, FDA believes that it is not necessary to establish limitations on the technical characteristics of CES devices within the definition.

#### IV. Proposed Reclassification

FDA is proposing that CES devices intended to treat insomnia and/or anxiety be reclassified from class III to class II. In order to reclassify these devices, the Agency must determine that there is sufficient information to establish special controls that, combined with the general controls, will provide a reasonable assurance of device safety and effectiveness. FDA has reconsidered the information before the Agency, including the deliberations of the 2012 Panel meeting and the reclassification petitions submitted for these devices, and has determined that there is sufficient information to establish special controls to effectively mitigate the risks to health identified in section V, and that these special controls, together with general controls, will provide a reasonable assurance of safety and effectiveness when applied to CES devices intended to treat insomnia and/or anxiety, including those existing legally marketed devices that have been previously cleared by FDA in 510(k)s.

Therefore, in accordance with sections 513(e) and 515(i) of the FD&C Act and § 860.130 (21 CFR 860.130), based on new information with respect to the devices and taking into account the public health benefit of the use of the device and the nature and known incidence of the risk of the device, FDA, on its own initiative, is proposing to reclassify this preamendments class III device into class II when the device is intended to treat insomnia and/or anxiety. FDA believes that this new information is sufficient to demonstrate that the proposed special controls can mitigate the risks to health identified in the next section, and that these special controls, together with general controls, will provide a reasonable assurance of safety and effectiveness for CES devices intended for treating insomnia and/or anxiety.



In this proposed order, the Agency has identified special controls under section 513(a)(1)(B) of the FD&C Act that, together with general controls (including prescription-use restrictions) applicable to the devices, are necessary to provide reasonable assurance of their safety and effectiveness.

Section 510(m) to the FD&C Act authorizes the Agency to exempt class II devices from premarket notification (510(k)) requirements. FDA has considered CES devices intended for treating insomnia and/or anxiety and decided that the device does require premarket notification. Therefore, the Agency does not intend to exempt this proposed class II device from premarket notification (510(k)) submission.

#### V. Risks to Health

After considering available information for the classification of CES devices intended to treat insomnia and/or anxiety, FDA has determined that the following risks to health are associated with use of the CES devices:

- Ineffective treatment--If the device is not effective and the patient is not treated in a conventional manner, the patient's psychological condition may worsen.
- Skin irritation--The electrodes or the conductive cream used with the electrodes may cause skin irritation.
- Headaches--Reported cases of adverse effects of CES devices include headaches following treatment with electrical stimulation.
- Dizziness--At higher levels of current, patients may experience feelings of dizziness that subside when the stimulation is turned down.
- Electrical shock and burns--Malfunction of the device may result in electrical shock or burns to the user.

## VI. Summary of Reasons for Reclassification

FDA believes that CES devices intended to treat insomnia and/or anxiety should be reclassified from class III to class II because, in light of new information about the effectiveness of these devices, special controls, in addition to general controls, can be established to provide reasonable assurance of safety and effectiveness of the device, and because general controls themselves are insufficient to provide reasonable assurance of its safety and effectiveness. FDA believes that the risks of the CES devices intended to treat insomnia and/or anxiety can be mitigated with special controls and that these mitigations will provide a reasonable assurance of safety for these devices. Based on a reconsideration of the available information and data, FDA believes that there is valid scientific evidence of effectiveness for CES devices in the treatment of insomnia and/or anxiety. However, because the information available to the Agency includes evaluations of different CES devices and the methodology of CES delivery (e.g., electrode placement, stimulation parameters, duration and frequency of treatment sessions) varies, the data are insufficient to determine adequate directions for use and warnings for unsafe use for specific devices, and to determine whether the devices when used in accordance with such directions will provide clinically meaningful results. Therefore, it cannot be concluded, based on available information alone, that there is a reasonable assurance of effectiveness for individual CES devices intended to treat insomnia and/or anxiety. However, the available information for the treatment of insomnia and/or generalized anxiety with CES devices is sufficient to develop special controls, that combined with general controls, can provide a reasonable assurance of safety and effectiveness.

## VII. Summary of Data Upon Which the Reclassification Is Based

FDA believes that the identified special controls, in addition to general controls (including prescription use restrictions and 510(k) notification requirements for devices that have not been legally marketed prior to the effective date of the final order, or devices that have been legally marketed but are required to submit a new 510(k) under § 807.81(a)(3) (21 CFR 807.81(a)(3)) because the device is about to be significantly changed or modified), will provide a reasonable assurance of safety and effectiveness of CES devices intended to treat insomnia and/or anxiety. Therefore, in accordance with sections 513(e) and 515(i) of the FD&C Act and § 860.130, based on new information with respect to the device and taking into account the public health benefit(s) of the use of the device and the nature and known incidence of the risk(s) of the device, FDA is proposing to reclassify these devices from class III to class II. The Agency has identified special controls that, when combined with general controls, are necessary to provide reasonable assurance of their safety and effectiveness.

There is a reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results (see § 860.7(e)(1)). During the 2012 Panel meeting (Ref. 1), the 2012 Panel expressed reservations on classifying CES devices into class III, given that there are limited safety concerns associated with these devices, and because they are not life-supporting or life-sustaining, or of substantial importance in preventing impairment of human health. The 2012 Panel also suggested that the list of significant risks in the 2011 proposed rule (76 FR 48062) was not accurate. There was consensus on the risks of skin irritation, headaches, and dizziness. However, the 2012 Panel did not believe that seizures and blurred vision were risks associated with CES, and also suggested

that worsening of the condition being treated, though of concern, could be adequately addressed by a patient being under the supervision of a medical professional. However, the 2012 Panel consensus was that, given the lack of adequate chronic effectiveness data, the benefits of the CES device did not outweigh the risks and the device should remain in class III as use of the device could present a potential unreasonable risk to health. FDA has reexamined the available information, however, including information made available after the 2012 Panel that confirms a level of effectiveness of CES treatment in certain indications, and believes that there is evidence of effectiveness for CES usage in treating patients with insomnia and/or anxiety.

The available information, while limited, consists of valid scientific evidence regarding CES use in treating insomnia and anxiety, which demonstrates basic effectiveness for some indications, as well as a low risk profile. In terms of safety, there is little evidence of device risk. FDA's own records (which include real-world clinical experience) indicate that only a very few adverse events have been reported over the past 10 years, and those reported have generally been minor in nature. It is also unclear how many of those events are attributable to use of the device. In the CES literature, 10 of the references reviewed reported no adverse events had occurred. Other studies reported a number of minor adverse events. More common adverse events reported in the literature include: Blurred vision, headaches, dizziness, tingling on the forehead, and increased situational anxiety. There are very limited reports of significant adverse events. In general, CES devices appear to have a favorable long-term safety profile. If properly manufactured and used as intended, FDA believes that the special controls identified in this proposed order, if finalized, together with general controls (including prescription-use restrictions and 510(k) notification requirements), are sufficient to mitigate the risks associated with CES devices intended to treat insomnia and/or anxiety.

The effectiveness of CES usage in the conditions studied, insomnia, depression, and anxiety, is more difficult to determine, as many of the studies reviewed did not use the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria to diagnose insomnia, depression, and anxiety. Some studies were also limited in terms of sample size, placebo effect (due to either no masking or unsuccessful masking), and inadequate statistical methods. Of the 39 papers included in the literature review presented at the 2012 Panel meeting (Ref. 2), some reported a beneficial effect of CES on certain indications while others demonstrated no effect. Furthermore, the body of research reviews 25 different models of CES devices used, excluding 7 that were custom built, and some studies did not report the CES device model. Because the electrical output characteristics vary across the different CES devices, it is difficult to definitively ensure the effectiveness of any one device. However, the Agency believes that the totality of the results of these studies do provide information on the general effectiveness of CES usage for insomnia and/or anxiety.

FDA's systematic assessment of the published literature, as presented to the 2012 Panel, included 30 studies for "on-label" CES use (tables 14 and 15 of the FDA Executive Summary) (Ref. 2). Study design and methodology varied across the published papers, several different CES devices were evaluated, and the methodology of CES delivery (e.g., electrode placement, stimulation parameters, duration and frequency of treatment sessions) also varied.

There were 24 studies that investigated the impact of CES on anxiety (11 randomized controlled trials (RCTs), 11 observational studies, 1 meta-analysis, and 1 systematic review). Of the RCTs that were evaluated, some trials reported a statistically significant benefit of CES treatment versus placebo in reducing anxiety symptoms (Refs. 3 through 8), while other studies demonstrated no difference in anxiety between the groups (Refs. 9 through 12). Feighner et al.

also conducted an RCT and reported a reduction in anxiety at 15 days after CES use, but this effect was no longer significant at 26 days (Ref. 13). The majority of observational studies reported a positive association between CES treatment and reduction in anxiety symptoms (Refs. 14 through 21). In the single-arm observational study by Bystritsky et al., improvements were reported for some but not all measures of anxiety (Ref. 22). Only two observational studies reported that CES did not have a significant impact on anxiety based on clinical assessment and standard inventories (Refs. 23, 24). A meta-analysis of eight RCTs evaluating the effectiveness of CES on anxiety indicated that CES versus sham treatment was associated with significantly improved anxiety (Ref. 25). Similar findings were reported in a systematic review that examined 34 controlled trials involving a total of 767 patients receiving CES and an additional 867 patients serving as controls (Ref. 26). Twenty six of 34 studies (77 percent) reported decreased anxiety after treatment with CES and the remaining 8 of 34 studies (24 percent) reported no such benefit.

FDA's assessment identified 18 studies that evaluated the effectiveness of CES on insomnia. Of the nine RCTs, some reported statistically significant reductions in insomnia symptoms in the CES group compared to placebo (Refs. 3, 4, 13, 27), while others reported no significant differences between the two groups (Refs. 9, 11, 12, 28). A study by Heffernan et al. also reported significant changes between the active CES treatment and placebo groups (Ref. 8). Among the eight observational studies, CES treatment was associated with less frequent (Ref. 15) and less intense (Ref. 18) sleep disturbances, less difficulty falling asleep (Refs. 29, 30), and feeling more rested in the morning (Ref. 29). Two observational studies reported no impact of CES on insomnia (Refs. 31, 32). In a study by Moore et al., subjective measures of insomnia were markedly improved during the first week of CES treatment but were no longer significant at 2 weeks (Ref. 23). A study by Nagata et al reported a significant reduction in sleep latency in

insomniacs but not in those without sleep disorders (Ref. 33). Lastly, a meta-analysis with pooled results from two RCTs examining the efficacy of CES for insomnia indicated no difference between the active CES use and sham groups (Ref. 25).

While the available scientific literature for insomnia and anxiety has shortcomings (as described previously) and no individual published study on CES provides definitive evidence of effectiveness of CES for the treatment of insomnia and/or anxiety, it is noteworthy that 18 of the 24 small published studies (those that enrolled fewer than 50 patients) that included assessments of insomnia and/or anxiety had a main finding that indicated a greater benefit of CES versus control for at least 1 of the outcome measures evaluated, and CES treatment group outcomes improved in all large published studies (although not all studies demonstrated improvement compared with control patients), including two studies identified after the 2012 Panel meeting (Refs. 34, 35). It is also worth noting that in a report on pain management (Ref. 36), the Army Surgeon General identifies CES as a potentially useful device for pain management, and argues that even treatments that may be associated with a placebo effect should be clinically exploited, given their effectiveness and safety margin. The report also states that gaps in evidence for such therapies exist due to lack of funded research. Based on the available information, it can be concluded that there is valid scientific evidence of effectiveness for CES in the treatment of insomnia and/or anxiety. Importantly, however, because different CES devices were evaluated and the methodology of CES delivery (e.g., electrode placement, stimulation parameters, duration and frequency of treatment sessions) varied, the data are insufficient to determine the technical performance parameters, adequate directions for use, and warnings for unsafe use for specific devices, and to determine whether the devices when used in accordance with such directions will provide clinically meaningful results. Therefore, it cannot be concluded, based on

available information alone, that specific CES devices will be effective for treating insomnia and/or anxiety. However, through general and special controls, it can be demonstrated that specific CES devices will provide clinically meaningful results.

FDA believes that these special controls should include clinical performance data that demonstrates that a device, when used as directed (including instructions for electrode placement, stimulation parameters, duration and frequency of treatment sessions, and other relevant characteristics), will provide clinically meaningful results in the indicated patient population for the intended use. It should be noted that the 2012 Panel asked during its meeting whether clinical data were available as a special control and was told that clinical data would likely not be collected if CES devices were classified in class II (Ref. 1). FDA has since reconsidered this point and believes that the totality of available information demonstrates general effectiveness of CES usage for insomnia and/or anxiety, but clinical data are necessary to demonstrate the clinical effect of specific devices for its labeled intended uses and specific stimulation parameters.

Based on its evaluation of the available information, FDA believes the proposed special controls identified in the next section, including clinical performance data, and in combination with the general controls, will provide reasonable assurance of safety and effectiveness for CES devices in the treatment of insomnia and/or anxiety.

#### VIII. Proposed Special Controls

FDA believes that the special controls in § 882.5800(b)(1), in addition to general controls (including applicable prescription-use restrictions and 510(k) notification requirements), address the risks to health and provide reasonable assurance of safety and effectiveness to mitigate the



risks to health described in section V for CES devices intended to treat insomnia and/or anxiety and provide a reasonable assurance of safety and effectiveness.

As discussed in the preceding section, each CES device has different technological characteristics, and although sufficient evidence is present to reasonably demonstrate a class effect, a reasonable assurance of the safety and effectiveness of specific CES devices from the existing data is not evident based upon differences in the technological and stimulation parameters for the CES devices. Therefore, FDA believes that additional clinical performance data are necessary to support premarket notifications (510(k)s) for these devices. The intended use population under investigation should correspond to a clinically recognized diagnosis, or symptomatology associated with that diagnosis, and sample sizes should provide adequate statistical power for a reasonable determination of effectiveness. The output and conditions of use (including electrode placement) in any clinical investigation used to support the 510(k) must demonstrate effectiveness for treating insomnia and/or anxiety. In instances where the device output and/or conditions of use are different from a predicate, the 510(k) should contain a complete study report that includes the protocol and clinical study results, including systematic collection of adverse events. A CES device in compliance with the special controls could be used as a benchmark. In instances where the technological and stimulation characteristics are identical, as identified in the labeling, it may be possible to leverage existing clinical data in lieu of providing results from a new clinical study.

A number of comments at the 2012 Panel meeting noted that worsening of a patient's condition during ineffective treatment is mitigated by adequate physician monitoring. FDA agrees with this assessment, and we believe that the labeling must include a warning regarding the need for physician monitoring. FDA also believes that the clinical data collected to support a

premarket notification will provide additional information to further characterize this risk and ensure that product labeling informs the user regarding appropriate use of the device and the patient population for which the device has sufficient performance to make a substantial equivalence determination.

The risks of skin irritation can be mitigated with biocompatibility testing to ensure that the materials used in patient-contacting components of the device are safe for skin contact as well as labeling that provides information on validated methods for reprocessing any reusable components between uses.

Headaches due to CES device use are typically transient and this risk can be mitigated by a warning that advises patients to reduce the level of stimulation or discontinue use of the device should a headache occur. The clinical data will also provide evidence regarding the stimulation parameters recommended for use during the study and the rate at which headaches occurred; the results and any observed adverse events must also appear in the labeling.

Some patients experience a feeling of dizziness at certain levels of stimulation. FDA believes this risk can be mitigated by a warning that advises patients to reduce the level of stimulation or discontinue use of the device if dizziness occurs, and to not drive or operate heavy machinery while using the device. The clinical data will also provide evidence regarding the stimulation parameters recommended for use during the study and the rate at which dizziness occurred; the results and any observed adverse events must also appear in the labeling.

Electrical shocks and burns, including unintended electric stimulation, pose risk to the patient. FDA believes this risk can be mitigated through appropriate electrical safety and electromagnetic compatibility (EMC) testing, and also through appropriate software verification, validation, and hazard analysis.

Table 1 shows how FDA believes that the risks to health identified in section V can be mitigated by the proposed special controls:

Table 1.--Health Risks and Mitigation Measures for CES for Insomnia and Anxiety

Identified Risk	Mitigation Measures
Ineffective treatment	Clinical Performance Testing Nonclinical (bench) performance testing Characterization and verification of technical parameters Labeling
Skin irritation	Biocompatibility testing Labeling
Headaches	Clinical performance testing Labeling
Dizziness	Clinical performance testing Labeling
Electrical shocks and burns	Electrical safety and EMC testing Software verification, validation, and hazard analysis

In addition, under 21 CFR 801.109, the sale, distribution, and use of these devices are restricted to prescription use. Prescription use restrictions are a type of general control in section 513(a)(1)(A)(i) of the FD&C Act. Under § 807.81, the device would continue to be subject to 510(k) notification requirements.

## IX. Dates New Requirements Apply

### A. CES Devices Intended to Treat Depression

In accordance with section 515(b) of the FD&C Act, FDA is proposing to require that a PMA be filed with the Agency for CES devices intended to treat depression. Under section 501(f)(2)(B) of the FD&C Act, PMAs for currently legally marketed CES devices intended to treat depression are required to be filed on or before 90 days after the effective date of a final order. However, for currently legally marketed CES devices intended to treat depression, FDA does not intend to enforce compliance with this 90-day deadline for an additional 90 days after

that deadline (i.e., 180 days after the effective date of any final order), as long as notice of intent to file a PMA is submitted within 90 days of the effective date of the final order. The notification of the intent to file a PMA submission should include a list of all model numbers for which a manufacturer plans to seek marketing approval through a PMA. FDA does not intend to enforce compliance with the PMA requirements with respect to an applicant of a currently legally marketed CES device intended to treat depression during FDA's review of the PMA. FDA intends to review any PMA for the device within 180 days of the date of filing. FDA cautions that under section 515(d)(1)(B)(i) of the FD&C Act, the Agency may not enter into an agreement to extend the review period for a PMA beyond 180 days unless the Agency finds that "the continued availability of the device is necessary for the public health." The following table shows the proposed regulatory timetable for currently legally marketed CES devices intended to treat depression.

Table 2.--Timetable for CES Devices Intended to Treat Depression

	Timetable for Which FDA Does Not Intend To Enforce Compliance (time after effective date of final order)	Distribution Period (time after effective date of final order)
Intent to file a PMA	90 days	Devices included in an intent to file: 180 days.
File a PMA	180 days	Devices not included in an intent to file: 90 days. Once PMA is filed, FDA does not intend to enforce compliance with PMA requirements until a not approvable decision or denial decision is issued; applicant may continue distribution if an approval order is issued.

FDA intends that under § 812.2(d), the preamble to any final order based on this proposal will state that, as of the date on which the filing of a PMA or a notice of completion of a PDP is required to be filed, the exemptions from the requirements of the IDE regulations for preamendments class III devices in § 812.2(c)(1) and (2) will cease to apply to any device that is (1) not legally on the market on or before that date or (2) legally on the market on or before that date but for which a PMA or notice of completion of a PDP is not filed by that date, or for which PMA approval has been denied or withdrawn.

If a PMA for a class III CES device is not filed with FDA within 90 days after the effective date of any final order requiring premarket approval for the device, the device would be deemed adulterated under section 501(f) of the FD&C Act. However, as explained previously, FDA does not intend to enforce compliance with this 90-day deadline for an additional 90 days after that deadline (i.e., 180 days after the effective date of any final order), as long as notice of intent to file a PMA is submitted within 90 days of the effective date of the final order.

The device may be distributed for investigational use only if the requirements of the IDE regulations are met. The requirements for significant risk devices include submitting an IDE application to FDA for its review and approval. An approved IDE is required to be in effect before an investigation of the device may be initiated or continued under § 812.30. FDA, therefore, cautions that IDE applications should be submitted to FDA at least 30 days before the end of the 90-day period after the effective date of the final order to avoid interrupting investigations. In conducting any clinical studies, CES devices intended to treat depression may be distributed for investigational use if the requirements of the IDE regulations (part 812) are met. There will be no extended period for filing an IDE nor exemption from IDE requirements, and studies may not be initiated without appropriate IDE approvals, where necessary.

### B. CES Devices Intended to Treat Insomnia and/or Anxiety

FDA proposes that the special controls identified in this proposed order take effect on the effective date of any final order, and CES devices intended to treat insomnia and/or anxiety must comply with the special controls following the effective date of the final order. However, FDA does not intend to enforce compliance with the special controls for currently legally marketed CES devices intended to treat insomnia and/or anxiety until 1 year after the effective date of the final order. FDA notes that a firm whose CES device was legally in commercial distribution before May 28, 1976, or whose device was found to be substantially equivalent to such a device and who does not intend to market such device for uses other than use in treating insomnia and/or anxiety, may remove such intended uses from the device's labeling. FDA proposes that for those manufacturers who wish to continue to offer for sale currently legally marketed CES devices intended to treat insomnia and/or anxiety, the manufacturers submit an amendment to their previously cleared 510(k)s for the devices within 1 year after the effective date of the final order that demonstrates compliance with the special controls. Such amendment will be added to the 510(k) file but will not serve as a basis for a new substantial equivalence review. A submitted 510(k) amendment in this context will be used solely to demonstrate to FDA that a CES device is in compliance with the special controls. If a 510(k) amendment for the device is not submitted within 1 year of the effective date of the final order or if FDA determines that the amendment does not demonstrate compliance with the special controls, then this compliance policy would not apply, and FDA would intend to enforce compliance with these requirements. In that case, the device is deemed adulterated under section 501(f)(1)(B) of the FD&C Act as of the date of FDA's determination of noncompliance or 1 year after the effective date of the final order, whichever is sooner.

For models of CES devices intended to treat insomnia and/or anxiety that have not been legally marketed prior to the effective date of the final order, or models that have been legally marketed but are subject to the requirement for a submission of a new 510(k) under § 807.81(a)(3) because the device is about to be significantly changed or modified, manufacturers must obtain 510(k) clearance, among other relevant requirements, and demonstrate compliance with the special controls included in the final order, before marketing the new or changed device.

#### X. Proposed Findings With Respect to Risks and Benefits

As required by section 515(b) of the FD&C Act, FDA is publishing its proposed findings regarding (1) the degree of risk of illness or injury designed to be eliminated or reduced by requiring that this device have an approved PMA or a declared completed PDP when intended for use in treating depression and (2) the benefits to the public from the use of CES devices for treating depression.

These findings are based on the reports and recommendations of the advisory committees (panels) for the classification of these devices along with information submitted in response to the FDA Order (74 FR 16214) that was issued under section 515(i) of the FD&C Act and any additional information that FDA has obtained. Additional information regarding the risks as well as classification associated with this device type can be found in 43 FR 55716, 44 FR 51770, 58 FR 45865, and 76 FR 48062.

#### XI. Device Subject to the Proposal to Require a PMA--CES Devices Intended To Treat Depression (§ 882.5800(c))

##### A. Identification

A cranial electrotherapy stimulator is a prescription device that applies electrical current that is not intended to induce a seizure to a patient's head to treat depression.

### B. Summary of Data

For treating depression, FDA concludes that the safety and effectiveness of CES devices have not been established by adequate scientific evidence. Given the FDA analysis and the advisory panel deliberations (Ref. 1), there is insufficient evidence of effectiveness for this indication. The panel recommended class III designation for CES devices in all indications, although as explained previously, FDA is proposing to reclassify CES when intended to treat insomnia and/or anxiety. The body of evidence is not sufficiently robust for FDA to determine that there is a reasonable assurance of safety and effectiveness for CES treatment of depression.

In the Agency's literature assessment, we identified 12 papers that examined the effect of CES on measures of depression (6 RCTs and 6 observational studies). In most RCTs, depression levels did not differ significantly between patients who were treated with active CES compared to those treated with placebo (Refs. 3, 9 through 11, 13), although one randomized trial by Hearst et al. reported fewer depression symptoms in the active CES treatment versus placebo groups (Ref. 12). Of the six observational studies that were reviewed, four studies reported improvement in depression symptoms after treatment with CES (Refs. 14, 15, 18, 19). Moore et al. also reported improvement in depression post- (versus pre-) CES treatment, but the findings were not statistically significant (Ref. 23). Moreover, the observational study by Marshall et al. reported no difference in depressive symptoms between the CES and placebo arms (Ref. 37).

Among the intended uses of insomnia, anxiety, and depression, the evidence supporting the effectiveness of CES for treating depression is the weakest. FDA believes that insufficient information exists regarding the risks and benefits of the device in order for FDA to determine



that general and/or special controls will provide reasonable assurance of the safety and effectiveness of CES for treating depression. As established in section 513(a)(1)(C) of the FD&C Act and 21 CFR 860.3(c)(3), a device is in class III if insufficient information exists to determine that general controls and/or special controls are sufficient to provide reasonable assurance of its safety and effectiveness and the device is purported or represented to be for a use that is life-supporting or life-sustaining, or for a use which is of substantial importance in preventing impairment of human health, or if the device presents a potential unreasonable risk of illness or injury. FDA believes that the risks to health identified in section V for the use of CES devices for treating depression, in the absence of an established positive benefit-risk profile, presents a potential unreasonable risk of illness or injury.

#### C. Risks to Health

The risks to health for CES devices for treatment of depression are the same as outlined in section V.

#### D. Benefits of CES Devices

As discussed previously, there is inadequate scientific evidence regarding the effectiveness of CES devices for treatment of depression, although the devices have the potential to benefit the public by providing an additional treatment option for depression.

### **XII. PMA Requirements for CES Devices Intended To Treat Depression**

A PMA for CES devices for treatment of depression must include the information required by section 515(c)(1) of the FD&C Act. Such a PMA should also include a detailed discussion of the risks identified previously, as well as a discussion of the effectiveness of the device for which premarket approval is sought. In addition, a PMA must include all data and information on: (1) Any risks known, or that should be reasonably known, to the applicant that

have not been identified in this document; (2) the effectiveness of the device that is the subject of the application; and (3) full reports of all preclinical and clinical information from investigations on the safety and effectiveness of the device for which premarket approval is sought.

A PMA must include valid scientific evidence to demonstrate reasonable assurance of the safety and effectiveness of the device for its intended use (see § 860.7(c)(1)). Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness. (§ 860.7(c)(2)).

### XIII. Opportunity to Request a Change in Classification

Before requiring the filing of a PMA or notice of completion of a PDP for a device, FDA is required by section 515(b)(2)(D) of the FD&C Act to provide an opportunity for interested persons to request a change in the classification of the device based on new information relevant to the classification. Any proceeding to reclassify the device will be under the authority of section 513(e) of the FD&C Act.

A request for a change in the classification of CES devices is to be in the form of a reclassification petition containing the information required by § 860.123, including new information relevant to the classification of the device.

### XIV. Codification of Orders

Prior to the amendments by FDASIA, section 513(e) of the FD&C Act provided for FDA to issue regulations to reclassify devices. Although section 513(e) as amended requires FDA to issue final orders rather than regulations, FDASIA also provides for FDA to revoke previously issued regulations by order. FDA will continue to codify classifications and reclassifications in the Code of Federal Regulations (CFR). Changes resulting from final orders will appear in the CFR as changes to codified classification determinations or as newly codified orders. Therefore, under section 513(e)(1)(A)(i), as amended by FDASIA, in this proposed order we are proposing to amend § 882.5800 by (1) revoking the requirements in § 882.5800(b) and (c) related to the classification of CES devices intended to treat insomnia and/or anxiety as class III devices and codifying the reclassification of CES devices intended to treat insomnia and/or anxiety to class II (special controls); and (2) retaining the requirements in § 882.5800(b) and (c) related to the classification of CES devices intended to treat depression as class III devices subject to PMAs, as described in section XII.

#### XV. Environmental Impact

The Agency has determined under 21 CFR 25.34(b) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

#### XVI. Paperwork Reduction Act of 1995

This proposed order refers to currently approved collections of information found in FDA regulations. These collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The collections of information in 21 CFR part 807, subpart E, have been approved under OMB control number 0910-0120; the collections of information in 21 CFR part 814, subpart B, have

been approved under OMB control number 0910-0231; and the collections of information under 21 CFR part 801 have been approved under OMB control number 0910-0485.

The effect of this order, if finalized, is to shift certain devices from the 510(k) premarket notification process to the PMA process. To account for this change, FDA intends to transfer some of the burden from OMB control number 0910-0120, which is the control number for the 510(k) premarket notification process, to OMB control number 0910-0231, which is the control number for the PMA process. As noted previously, FDA estimates that it will receive three new PMAs as a result of this order, if finalized. Based on FDA's most recent estimates, this will result in a 1,040-hour burden increase to OMB control number 0910-0231. FDA also estimates that there will be three fewer 510(k) submissions as a result of this order, if finalized. Based on FDA's most recent estimates, this will result in a 136-hour burden decrease to OMB control number 0910-0120. Therefore, on net, FDA expects a burden hour increase of 904 hours due to this proposed regulatory change.

#### XVII. Proposed Effective Date

FDA proposes that any final order based on this proposal become effective on the date of publication of the final order in the Federal Register or at a later date if stated in the final order.

#### XVIII. Comments for Previous Dockets

Comments submitted to the previous dockets (2011-N-0504, 2013-N-0195) have been officially noted and do not need to be resubmitted. FDA has considered previous docket comments before issuing this proposed order.

#### XIX. References

The following references are on display in the Division of Dockets Management (see ADDRESSES) and are available for viewing by interested persons between 9 a.m. and 4 p.m.,

Monday through Friday; they are also available electronically at <http://www.regulations.gov>.

FDA has verified the Web site addresses, as of the date this document publishes in the Federal Register, but Web sites are subject to change over time.

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<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/NeurologicalDevicesPanel/UCM335752.pdf>.
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List of Subjects in 21 CFR Part 882

Medical devices, Neurological devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 882 be amended as follows:

PART 882--NEUROLOGICAL DEVICES

1. The authority citation for 21 CFR part 882 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 371.

2. Revise § 882.5800 to read as follows:

§ 882.5800 Cranial electrotherapy stimulator.

(a) Identification. A cranial electrotherapy stimulator is a prescription device that applies electrical current that is not intended to induce a seizure to a patient's head to treat psychiatric conditions.

(b) Classification. (1) Class II (special controls) when intended to treat insomnia and/or anxiety. The special controls for this device are:

(i) A detailed summary of the clinical testing pertinent to use of the device to demonstrate the effectiveness of the device when intended to treat insomnia and/or anxiety.

(ii) Components of the device that come into human contact must be demonstrated to be biocompatible.

(iii) The device must be designed and tested for electrical safety and electromagnetic compatibility (EMC) in its intended use environment.

(iv) Appropriate software verification, validation, and hazard analysis must be performed.

(v) The technical parameters of the device, including waveform, output mode, pulse duration, frequency, train delivery, maximum charge and energy, must be fully characterized and verified.

(vi) The labeling for the device must include the following:

(A) The intended use population and the intended use environment.

(B) A warning that patients should be monitored by their physician for signs of worsening.

(C) A warning that instructs patients on how to mitigate the risk of headaches, and what to do should a headache occur.

(D) A warning that instructs patients on how to mitigate the risk of dizziness, and what to do should dizziness occur.

(E) A detailed summary of the clinical testing, which includes the clinical outcomes associated with the use of the device, and a summary of adverse events and complications that occurred with the device.

(F) Instructions for use that address where to place the electrodes, what stimulation parameters to use, and duration and frequency of treatment sessions. This information must be based on the results of clinical studies for the device.

(G) A detailed summary of the device technical parameters, including waveform, output mode, pulse duration, frequency, train delivery, and maximum charge and energy.

(H) Information on validated methods for reprocessing any reusable components between uses.

(vii) Cranial electrotherapy stimulator devices marketed prior to the effective date of this reclassification must have an amendment submitted to the previously cleared premarket notification (510(k)) demonstrating compliance with these special controls.

(2) Class III (premarket approval) when intended to treat depression.

(c) Date premarket approval application (PMA) or notice of completion of product development protocol (PDP) is required. A PMA or notice of completion of a PDP is required to be filed with the Food and Drug Administration on or before [A DATE WILL BE ADDED 90 DAYS AFTER DATE OF PUBLICATION OF A FUTURE FINAL ORDER IN THE FEDERAL REGISTER], for any cranial electrotherapy stimulator device with an intended use described in (b)(3) of this section, that was in commercial distribution before May 28, 1976, or that has, on or before [A DATE WILL BE ADDED 90 DAYS AFTER DATE OF PUBLICATION OF A FUTURE FINAL ORDER IN THE FEDERAL REGISTER], been found to be substantially equivalent to any cranial electrotherapy stimulator device with an intended use described in paragraph (b)(3) of this section, that was in commercial distribution before May 28, 1976. Any other cranial electrotherapy stimulator device with an intended use described in paragraph (b)(3) of this section shall have an approved PMA or declared completed PDP in effect before being placed in commercial distribution.

Dated: January 15, 2016.

Leslie Kux,

Associate Commissioner for Policy.

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